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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,723	01/11/1999	TAKANORI OKA	171-613P	8292

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EXAMINER

SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/214,723

Applicant(s)

OKA, TAKANORI

Examiner

Bradley L. Sisson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 April 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 3-5, 7, 8 and 13-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 3-5, 7, 8 and 13-15 is/are rejected.
- 7) ☒ Claim(s) 3-5, 7 and 8 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Claim Objections

1. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim. In the present case, claims 3-5, 7, and 8 depend from succeeding claim 13.

2. A claim, which depends from a dependent claim, should not be separated by any claim, which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5, 7, 8, and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' "*Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513

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(Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, e.g., *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

For convenience, claims 13 and 15 are reproduced below.

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13. (Five Times Amended) A nucleic acid assay process for identifying and/or quantifying a mutation or polymorphism in a double stranded sample DNA prepared by amplification of a particular region of an analyte nucleic acid using PCR method which is present in a specimen, comprising the steps of:

providing labeled standard DNA having a nucleotide sequence the same as a mutated or polymorphic target DNA of interest, wherein said labeled standard DNA comprises a double stranded nucleic acid having a site capable of binding to a solid support on one strand and a detectable label on the other strand;

amplifying said particular region of said analyte nucleic acid which is present in said specimen to prepare said double stranded sample DNA for competitive hybridization, wherein said sample DNA comprises both mutated or polymorphic target DNA and wild-type DNA in an amplifiable amount;

selecting a detection limit for said mutated or polymorphic target DNA, wherein when the detection limit for the target DNA present in said sample DNA is A/B , the excessiveness of said sample DNA is at least B/A , and wherein A/B is the fractional equivalent of the percentage of said mutated or polymorphic target DNA content in the sample DNA;

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adding an excessive amount of said sample DNA to said labeled standard DNA, to allow competitive hybridization to take place between said mutated or polymorphic target DNA and labeled standard DNA under conditions which allow for hybridization of at least some of said labeled standard DNA and under conditions wherein non-target sample DNA does not hybridize with said labeled standard DNA, wherein the excessiveness of said sample DNA added to said labeled standard DNA in the competitive hybridization is calculated as the value of B/A ,

detecting the hybridized labeled standard DNA by utilizing said detectable label and said site capable of binding to a solid support; and

evaluating the degree of exchange that occurred during competitive hybridization of the complementary strands between said sample DNA and said labeled standard DNA.

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15. A nucleic acid assay process for identifying and/or quantifying a mutation or polymorphism in a double stranded sample DNA, comprising the steps of:

providing labeled standard DNA having a nucleotide sequence the same as a mutated or polymorphic target DNA of interest, wherein said labeled standard DNA comprises a double stranded nucleic acid having a site capable of binding to a solid support on one strand and a detectable label on the other strand;

amplifying a particular region of an analyte nucleic acid to prepare said double stranded sample DNA for competitive hybridization, wherein said sample DNA comprises both mutated or polymorphic target DNA and wild-type DNA in an amplifiable amount;

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selecting a theoretical value in μg for the amount of said mutated or polymorphic target DNA in said sample DNA, wherein the amount in μg of said mutated or polymorphic target DNA is expressed as A, and the total amount in μg of said sample DNA is B, such that A/B is the fractional equivalent of the percentage of said mutated or polymorphic target DNA content in the sample DNA;

adding an excessive amount in μg of said sample DNA to said labeled standard DNA, which is calculated as the value of B/A ;

allowing competitive hybridization to take place between said mutated or polymorphic target DNA and labeled standard DNA under conditions wherein said wild-type DNA does not hybridize with said labeled standard DNA,

detecting the hybridized labeled standard DNA by utilizing said detectable label and said site capable of binding to a solid support; and

evaluating the degree of exchange that occurred during competitive hybridization of the complementary strands between said sample DNA and said labeled standard DNA.

4. It is clear from the claims that the skilled artisan is to perform amplification reactions as well as hybridization reactions. The claims place no restriction on the size of the template or amplicons, and no restriction is placed on the number of cycles of amplification that is to take

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place. The claims have been interpreted as encompassing virtually any detection limit. While claim 15 defines the units of measure (micrograms), no detection limit is set.

5. For purposes of examination, the DNA to be detected from virtually any source, including cells from any single or multicellular life form, as well as DNA or cDNA from viruses.

The area of art to which the invention belongs has advanced to the point that numerous difficulties have been identified. In support of this position, attention is directed to the following documents.

US Patent Application Publication 2003/0194697 A1 teaches:

Direct detection of viral DNA or RNA in clinical samples can be achieved using PCR and specific primers tailored for the virus of interest. Since PCR involves an amplification step, cross-contamination is a major problem and it is difficult to establish reliable quantitative methods. (Emphasis added)

US Patent Application Publication 2003/0190604 (Zhang et al.) teaches:

[0006] One of the most difficult problems is preparation of the target nucleic acid prior to carrying out its amplification and detection. This process is time and labor intensive and, thus, generally unsuitable for a clinical setting, where rapid and accurate results are required. Another problem, especially for PCR and SDA, is that conditions for amplifying the target nucleic acid for subsequent detection and optional quantitation vary with each test, i.e., there are no constant conditions favoring test standardization. This latter problem is especially critical for the quantitation of a target nucleic acid by competitive PCR and for the simultaneous detection of multiple target nucleic acids.

The claimed method places no restriction on the size of the reaction volumes and as such, the claimed method fairly encompasses situations where one is attempting to quantify DNA where no molecule is present in the aliquot of the sample that is to undergo amplification, yet is present in the crude starting material. US Patent Application Publication 2003/0186246 A1 teaches in paragraph 79:

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If one were to reduce the volume of this PCR reaction 100-fold from 10 μ l to 100 nanoliters, genes expressed 10,000-fold lower than β -actin would be represented by 0.6 molecules or fewer which, due to stochastic considerations, would be difficult to quantify with acceptable confidence.

Chan (US Patent Application Publication US 2002/0119455 A1):

[0018] In practice, Probe Up methods have been used to generate sequences of about 100 base pairs. Imperfect hybridization has led to difficulties in generating adequate sequence. Error in hybridization is amplified many times. A 1% error rate reduces the maximum length that can be sequenced by at least 10%. Thus if 1% of 65,536 oligonucleotides gave false positive hybridization signals when hybridizing to a 200-mer DNA target, 75% of the scored "hybridizations" would be false (Bains, 1997). Sequence determination would be impossible in such an instance. The conclusion is that hybridization must be extremely effective in order to generate reasonable data. Furthermore, sequencing by hybridization also encounters problems when there are repeats in sequences that are one base less than the length of the probe. When such sequences are present, multiple possible sequences are compatible with the hybridization data. (Emphasis added.)

The claimed method fairly encompasses performing any number of cycles of amplification.

Accordingly, the number of rounds can be as few as 1 cycle, or as many as infinity. US Patent Application Publication 2003/0175684 A1 teaches that problems arise as a direct result of the number of cycles of amplification:

[0011] Most of the semiquantitative assays are based on standard PCR analysis of a dilution series of patient samples compared to a known standard. While extremely useful, quantitative PCR can be very laborious to perform. Most of the difficulties arise because only a very small number of the cycles in a PCR reaction contain useful information. The early cycles have undetectable amounts of the DNA product and late cycles (plateau phase) are almost as uninformative. (Emphasis added)

As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

- The purity of the nucleic acid preparation.

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- Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.
- Length of homologous base sequences- any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.
- Ionic strength- the rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.
- Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.
- Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.
- Denaturing reagents- the presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.
- Incubation- the longer the incubation time, the more complete will be the hybridization.
- Volume exclusion agents- the presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

- Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

6. A review of the disclosure fails to locate where the instant disclosure has taught the skilled artisan how to overcome these issues. Accordingly, the public would be forced to perform trial-and-error experimentation for an indeterminable period in an attempt to practice the full scope of the claims. As evidenced above, many problems are known to exist, even at this date, which is several years post filing. Accordingly, the skilled artisan would have little expectation of ever being able to practice the full scope of the claimed invention. Such experimentation is clearly undue.

7. In view of the breadth of scope claimed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed non-enabled by the disclosure.

8. Claim 15 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. A review of the disclosure fails to locate where support can be found for the limitation that one is to select “a theoretical value in μg for the amount of said mutated or polymorphic target DNA (emphasis added).

Conclusion

9. Rejections that appeared in the prior Office action and which were not repeated hereinabove have been withdrawn.
10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
11. A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.
13. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

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14. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read "B. L. Sisson".

Bradley L. Sisson
Primary Examiner
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BLS
17 November 2003